1. (Amended) A method for the treatment of metanephric tissue for transplantation into a recipient comprising contacting said metanephric tissue, in vitro, with a growth factor-containing composition comprising one or more growth factors for metanephric development and transplanting said metanephric tissue into said recipient.

REMARKS

Claims 1, 4, 5, 7-9,17, 20 and 22-24 are pending. A version with markings to show changes made to the claims and an appendix of pending claims, as amended, are attached for the Examiner's convenience.

Claim 1 has been amended to indicate that after the metanephric tissue is treated with one or more growth factors, it is transplanted into a recipient.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claim 9 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite on the grounds that the claim does not particularly point out or distinctly claim the subject matter of the invention. More particularly, the Examiner argues that Claim 9 does not recite a specific mode of administration.

Claim 9 recites a method of treatment of metanephric tissue comprising contacting the metanephric tissue, *in vivo,* with a growth-factor containing composition comprising one or more growth factors for metanephric development at the time of or after being transplanted into the recipient, wherein the growth-factor containing composition is administered to the recipient in a manner such that one or more growth factors for

metanephric development are present in the recipient's blood which circulates through the metanephric tissue.

Applicant respectfully traverses the rejection.

Applicant directs the Examiner's attention to Example 5 (page 17, lines 29-31), which describes a method of administering growth-factors to animal recipients by Alzet pump infusion (*e.g.*, 60 μg/day/animal). Applicant notes that other methods of administration which are well known in the art can additionally be used for administering growth factors to animal hosts, including but not limited to, delivery using a variety of osmotic pumps wherein the size, pumping rate, and pumping duration of the osmotic pumps are variable.

For the foregoing reasons, the Examiner's rejection under 35 U.S.C. §112, second paragraph) of claim 9 should be withdrawn.

Claim Rejections - 35 U.S.C. §102(a) As Being Anticipated by *Sariola, et al.*

Claim 1 (and claims 4-5 which depend therefrom) stand rejected under 35 U.S.C. §102(a) as being anticipated by *Sariola, et al* (WO 97/49798).

Claim 1 has been amended to recite a method for treatment of metanephric tissue for transplantation into a recipient comprising contacting the metanephric tissue, *in vitro*, with a growth-factor-containing composition comprising one or more growth factors for metanephric development and transplanting the metanephric tissue into the recipient.

The Examiner argues that Applicant's invention is anticipated by the glial cell line derived neurotrophic factor ("GNDF") growth factor which is described as inducing formation of uteric buds from Wolffian duct tissue. More specifically, the Examiner

argues that GNDF induces cellular growth in the region of the metanephros and Applicant's claims reciting induced metanephric tissue are anticipated by this teaching. The Examiner further argues that although *Sariola* does not teach transplantation, the transplantation language recited in Applicant's claims is an "intended use limitation." The Examiner cites *In re Best* and *In re Spada* in support of this assertion.

Applicant respectfully traverses the rejection.

Applicant notes that *Sariola* teaches GNDF induced ureteric budding of Wolffian duct tissue. Applicant's invention, in contrast, teaches growth, proliferation and/or differentiation (page 4, line 31) of metanephric tissue induced by one or more growth factors. Applicant's claims recite a growth factor for metanephric development rather than budding of Wolffian duct tissue. Further Applicant notes that Wolffian duct tissue is distinct from Applicant's metanephric tissue in that Wolffian duct tissue degenerates *in vivo* in mammalian females and forms sperm carrying ducts in mammalian males. The metanephric tissue claimed by Applicant is not demonstrated to exhibit these properties. Moreover, the *Sariola* ureteric buds are distinct from the developed metanephric tissue claimed by Applicant. Ureteric bud tissue arises from induced mesonephric Wolffian duct tissue and stimulates development of metanephric tissue as part of kidney organogenesis. The metanephric tissue in the claimed invention is not derived from mesonephric Wolffian duct tissue and is induced *in vitro* by one or more growth factors which are specifically demonstrated to stimulate metanephric development. In summary, neither the *Sariola* Wolffian duct tissue nor the *Sariola* ureteric bud tissue are components of Applicant's invention.

In addition, the *Sariola* reference neither demonstrates nor provides experimental data indicating that GNDF would be useful for inducing metanephric development of Applicant's metanephric tissue. The skilled artisan thus has no rational basis for believing the *Sariola* GNDF would be operable in Applicant's invention to promote the development of metanephric tissue. Applicant's invention requires the specific combination of metanephric tissue and one or more growth factors demonstrated to induce metanephric development. In particular, Applicant's claims 1, 4, and 5 require contacting metanephric tissue, *in vitro,* with one or more growth factors demonstrated to stimulate metanephric development and transplanting the developed metanephric tissue. A prior art reference which fails to disclose a growth factor demonstrated to induce development of native metanephros does not anticipate Applicant's claims. The GNDF and Wolffian duct combination disclosed in *Sariola* do not operate by the same mechanisms, exhibit the same properties, or produce the same *in vitro* differentiated product, as the metanephric tissue and growth factor combination described by Applicant. Accordingly, Applicant's claims are not anticipated by the *Sariola* reference.

Claim 1 has been amended to recite that the growth factor treated metanephric tissue is thereafter transplanted into a recipient. *Sariola* does not teach transplantation. Since not all of the limitations recited in Applicant's claims are disclosed in *Sariola*, Applicant's claims are not anticipated by the reference. Moreover, Applicant's developed metanephric tissue is not "identical or substantially identical in structure or composition" to the *Sariola* differentiated Wolffian duct tissue. The differentiated metanephric tissue claimed by Applicant is produced by contacting metanephric tissue with one or more growth factors specifically operable for inducing metanephric development. The process

by which metanephric tissue becomes developed is thus distinct from the process by which the *Sariola* ureteric buds are induced from Wolffian duct tissue.

For the foregoing reasons, the Examiner's rejection under 35 U.S.C. §102(a) of amended claim 1 (and claims 4-5 which depend therefrom) should be withdrawn.

Claim Rejections - 35 U.S.C. §102(b)– *Liu*, et al.

Claim 1 (and claims 4-5 which depend therefrom) stand rejected under 35 U.S.C. §102(b) as being anticipated by *Liu, et al.*

The Examiner argues that the differentiated metanephric tissue induced by one or more growth factors claimed by Applicant is anticipated by the mouse metanephroi disclosed in *Liu* as increasing in size due to exposure to organ culture containing IGF-I growth factor.

The Examiner argues that although *Liu* does not teach transplantation, the "transplantation" language recited in Applicant's claims is an "intended use limitation."

Applicant respectfully traverses the rejection.

Applicant points out that the mouse metanephroi disclosed in *Liu* were contacted with organ culture containing IGF-I growth factor for a period of 7 days. Subsequent to exposure, the metanephroi were observed to increase in size. Applicant notes that the metanephric tissue recited in Applicant's claims was contacted by exogenous administration of one or more growth factors specifically demonstrated to stimulate metanephric tissue development. Applicant's metanephric tissue is induced by exposure to growth factors, rather than to organ culture. Moreover, the abstract fails to demonstrate which components of the *Liu* organ culture actually produce metanephroi enlargement.

Applicant observes that it is not uncommon for tissue to grow when it is placed in a nutrient culture for 7 days, irrespective of the presence of IGF-I in the medium. Moreover, the *Liu* abstract fails to provide assays, data, or experimental results demonstrating that IGF-I is specifically responsible for inducing metanephroi enlargement. In addition, Applicant's independent claims 4 and 5 limit contact between Applicant's metanephric tissue and growth factor-containing composition to less than 8 hours, and to less than 2 hours, respectively. *Liu* fails to disclose this limitation. Finally, because *Liu* provides no assays, data, or experimental results demonstrating that IGF-I induces the enlargement of metanephroi, the reference is non-enabling and cannot be meritoriously cited as a 102(b) reference against Applicant.

Claim 1 has been amended to recite that the metanephric tissue has been treated with a growth factor *in vitro* which is thereafter transplanted into a recipient. *Liu* does not teach or describe transplantation. Since not all of the limitations recited in Applicant's claims are disclosed in *Liu*, the reference does not anticipate Applicant's claims.

For these reasons, the Examiner's rejection under 35 U.S.C. §102(b) of amended claim 1 (and claims 4-5 which depend therefrom) should be withdrawn.

Claim Rejections - 35 U.S.C. §102(b)– *Rogers*, et al.

Claim 1 (and claims 4-5 which depend therefrom) stand rejected under 35 U.S.C. §102(b) as being anticipated by *Rogers, et al.*

The Examiner argues that the developed metanephric tissue recited in Applicant's claims is anticipated by the *Rogers* metanephroi, which increase in size and morphology in the presence of exogenously administered TGF-α. The Examiner further argues that

although *Rogers* does not teach transplantation, the "transplantation" language recited in Applicant's claims is an "intended use limitation."

Applicant respectfully traverses the rejection.

Applicant notes that the TGF-α growth factor disclosed in *Rogers* is endogenously produced by metanephroi which are grown in a chemically defined organ culture. Applicant's claims are distinguished from *Rogers* in that Applicant teaches treatment of metanephric tissue with a solution containing one or more exogenously administered growth factors which are specifically demonstrated to induce metanephric tissue development. The growth factors recited in Applicant's claims are exogenously administered, rather than endogenously produced.

Applicant further notes that *Rogers* teaches exposure of metanephroi to an organ culture containing endogenously produced TGF-α, but fails to demonstrate that TGF-α specifically induces changes in the metanephroi size and morphology. Applicant observes that it would not be unusual for metanephric tissue grown in organ culture for up to 6 days to increase in size and change in morphology, irrespective of the presence of TGF-α. In addition, *Rogers* fails to provide assays, data, or experimental results demonstrating that TGF-α is specifically responsible for inducing the metanephroi size and morphology changes. Further, Applicant's independent claims 4 and 5 limit contact between the metanephric tissue and growth factor-containing composition to periods of less than 8 hours, and to periods of less than 2 hours, respectively. *Rogers* fails to disclose this limitation.

Finally, because *Rogers* provides no assays, data, or experimental results demonstrating that TGF-α is specifically responsible for inducing the size and morphology

changes in metanephroi, the reference is non-enabling and cannot be meritoriously cited as a 102(b) reference against Applicant.

Applicant additionally points out that the transplantation limitation of amended claim 1 overcomes the Examiner's "intended use" argument.

For the foregoing reasons, the Examiner's rejection under 35 U.S.C. §102(b) of amended claim 1 (and claims 4-5 which depend therefrom) should be withdrawn.

Claim Rejections - 35 U.S.C. §103(a) (*Hammerman et al.* in view of *Liu et al*)

Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom) stand rejected under 35 U.S.C. §103(a) as being unpatentable under *Hammerman* in view of *Liu.*

Claim 7 recites a method for treatment of metanephric tissue transplanted into a recipient comprising contacting the transplanted tissue with a growth factor-containing composition comprising one or more growth factors for metanephric development, wherein the growth factor-containing composition is administered to the transplanted metanephric tissue at the time a ureteroureterostomy is performed.

Claim 22 recites a method for treatment of metanephric tissue comprising contacting the metanephric tissue, *in vivo*, with a growth factor-containing composition comprising one or more growth factors for metanephric development at the time of or after being transplanted into the recipient.

The Examiner argues that Applicant's invention would be obvious to the ordinarily skilled artisan in light of *Hammerman* in view of *Liu*. More specifically, the Examiner alleges that *Hammerman* teaches a method of increasing the nephron mass of a

mammalian recipient comprising implanting at least one whole metanephros of an embryonic mammalian donor next to the recipient's omentum, while *Liu* teaches enlargement of metanephroi induced by the administration of IGF-I growth factor. The Examiner concludes that it would be obvious for the skilled artisan to exogenously administer IGF-I subsequent to metanephros transplantation for inducing metanephroi growth and differentiation.

Applicant respectfully traverses the rejection.

Applicant notes that *Hammerman* teaches transplantation of whole metanephros under conditions permitting metanephros vascularization and the formation of mature chimeric kidney capable of producing and externalizing urine. Applicant's claim 7, in contrast, recites transplanted metanephric tissue contacted *in vivo* by one or more growth factors at the time of performance of a ureteroureterostomy. *Hammerman* does not teach the *in vivo* administration of one or more growth factors at the time of ureteroureterostomy, as recited in claim 7. Moreover, *Liu* does not cure the deficiencies of *Hammerman* since *Liu* only discloses the *in vitro* administration of IGF-I growth factor.

Claim 22 recites transplanted metanephric tissue contacted *in vivo* by one or more growth factors for metanephric development at the time of or subsequent to transplantion. Although the Examiner cites *Liu* as teaching growth factor induced development of metanephric tissue, Applicant notes the reference teaches *in vitro*, rather than *in vivo*, contact with IGF-I. Moreover, as previously stated herein, *Liu* fails to demonstrate that IGF-I is specifically responsible for inducing metanephroi enlargement.

For the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103 and Applicant requests reconsideration and withdrawal of the outstanding rejections of Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom).

Claim Rejections - 35 U.S.C. §103(a) (*Hammerman et al.* in view of *Rogers et al*)

Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom) stand rejected under 35 U.S.C. §103(a) as being unpatentable under *Hammerman* in view of *Rogers.*

The Examiner argues that Applicant's invention would be obvious to the ordinarily skilled artisan in light of *Hammerman* in view of *Rogers*. More specifically, the Examiner alleges that *Hammerman* teaches implantation of metanephroi, while *Rogers* teaches contact with TGF-α growth factor for increasing metanephroi size and morphology. The Examiner concludes that it would have been obvious for the skilled artisan to administer exogenous TGF-α subsequent to transplantation for inducing the growth and differentiation of metanephroi.

Applicant respectfully traverses the rejection.

Applicant relies on the arguments previously recited herein. *Hammerman* does not disclose the *in vivo* administration of one or more growth factors at the time of ureteroureterostomy or during or after transplantation. *Rogers* teaches organ culture containing endogenously produced TGF-α growth factor, rather than the exogenously administered growth factors recited in Applicant's claims. Moreover, the *Rogers* abstract fails to demonstrate that TGF-α is specifically responsible for inducing the *in vitro*

increase in metanephroi size and change in morphology. The TGF-α disclosed in *Rogers* is produced *in vitro*, rather than exogenously administered *in vivo*, as recited in Applicant's claims. Therefore *Rogers* in combination with *Hammerman* does not render the claims obvious.

For the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. Applicant respectfully requests reconsideration and withdrawal of the outstanding rejections of Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom).

Claim Rejections - 35 U.S.C. §103(a) (*Woolf et al.* in view of *Rogers et al*)

Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom) stand rejected under 35 U.S.C. §103(a) as being unpatentable under *Woolf* in view of *Rogers*.

The Examiner argues that Applicant's invention would be obvious to the ordinarily skilled artisan in light of *Woolf* in view of *Rogers*. More specifically, the Examiner alleges that *Woolf* teaches implantation of metanephric tissue into recipients, while *Rogers* teaches administration of TGF-α growth factor for inducing changes in metanephroi size and morphology. The Examiner concludes that it would have been obvious for the skilled artisan to exogenously administer TGF-α subsequent to transplantation for inducing metanephroi growth and differentiation.

Applicant respectfully traverses the rejection.

Applicant notes that *Woolf* teaches implanted metanephric tissue which forms chimeric kidney. Applicant's claim 7, in contrast, recites transplanted metanephric tissue

contacted *in vivo* by one or more growth factors at the time of performance of a ureteroureterostomy. Applicant notes that *Woolf* fails to teach the use of any growth factor, much less treatment with a growth factor, at the time a ureteroureterostomy is performed or during or after transplantation.

Applicant's claim 22 recites transplanted metanephric tissue contacted *in vivo* by one or more growth factors for metanephric development at the time of or subsequent to transplantation. As discussed herein, *Woolf* does not teach the use of growth factors. Applicant reiterates that *Rogers* teaches *in vitro* organ culture containing endogenously produced TGF-α growth factor, rather than the exogenous administration of one or more growth factors. In addition, *Rogers* fails to demonstrate that TGF-α is specifically responsible for inducing changes in metanephroi size and morphology. Finally, the TGF-α disclosed in *Rogers* is endogenously produced *in vitro*, rather than exogenously administered *in vivo,* as are the growth factors recited in Applicant's claims. Thus the combination of *Woolf* and *Rogers* does not teach all of the limitations set forth in the claims.

For the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103 and Applicant respectfully requests reconsideration and withdrawal of the outstanding rejections of Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom).

Claim Rejections - 35 U.S.C. §103(a) (*Woolf et al.* in view of *Liu et al*)

Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom) stand rejected under 35 U.S.C. §103(a) as being unpatentable under *Woolf* in view of *Liu.*

The Examiner argues that Applicant's invention would be obvious to the ordinarily skilled artisan in light of *Woolf* in view of *Liu.* More specifically, the Examiner alleges that *Woolf* teaches implantation of metanephric tissue into recipients, while *Liu* teaches enlargement of metanephroi induced by the administration of IGF-I growth factor. The Examiner concludes that it would be obvious for the skilled artisan to exogenously administer IGF-I subsequent to metanephros transplantation for inducing metanephroi growth and differentiation.

Applicant respectfully traverses the rejection.

Applicant's arguments in opposition to *Woolf* and *Liu* have been previously recited herein. Applicant reiterates that *Liu* teaches *in vitro*, rather than *in vivo,* contact with IGF-1. Moreover, as previously stated herein, *Liu* fails to demonstrate that IFG-1 is specifically responsible for inducing metanephroi enlargement.

For the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103 and Applicant respectfully requests reconsideration and withdrawal of the outstanding rejections of Claims 7 (and claim 17 and 20 which depend therefrom) and 22 (and claims 8, 9, 23 and 24 which depend therefrom).

Based on the foregoing, it is submitted that claims 1, 4, 5, 7-9,17, 20 and 22-24 are patentable over the art of record.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and an early notification of such is solicited. If upon, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR, HOHBACH, TEST,
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By: _____
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VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Amended) A method for the treatment of metanephric tissue for transplantation into a recipient comprising contacting said metanephric tissue, in vitro, with a growth factor-containing composition comprising one or more growth factors for metanephric development [prior to] and transplanting said metanephric tissue into said recipient.